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Literature Review Examining Continuous Subcutaneous Insulin Infusion and Effects on
Hemoglobin A1c, Hypoglycemia, Hyperglycemia/Diabetic Ketoacidosis, and Quality of Life

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Literature Review Examining Continuous Subcutaneous Insulin Infusion and Effects on Hemoglobin A1c, Hypoglycemia, Hyperglycemia/Diabetic Ketoacidosis, and Quality of Life

Chapter 1: Introduction

Diabetes is a life altering disease that can affect children at any age. If diabetes is not properly controlled, it can lead to severe health problems and even death. An autoimmune response in the body that targets and destroys the beta cells in the pancreas is responsible for the development of Type I diabetes in children. Since 1921 researchers have studied the disease process and to this point there are no answers why this occurs or how to prevent this disease from happening. The end result of the autoimmune response for children diagnosed with diabetes is to replace their lack of insulin production either with multiple daily injections (MDI) with insulin or continuous subcutaneous insulin infusion (CSII) via insulin pump (Buttaro, Trybulski, Bailey, & Sandberg-Cook, 2008).

Diabetes can be defined as type I or type II diabetes. Type I diabetes requires at least two insulin injections. Type II diabetes treatment can consist of either oral glucose lowering medications and/or insulin. It is noted that the incidence of type I diabetes children continues to rise in the United States. About one in every 400 children and adolescents has type I diabetes. The percentage of new cases for type I diabetes each year is 19.7 % per 100,000 for individuals younger than 10 years of age and 18.6 % per 100,000 for individuals older than 10 years of age according to the National Diabetes Statistics by the National Institutes of Health (2011). The Center for Disease Control's (CDC's) National Diabetes Fact Sheet (2011) found that over 25 % of people younger than 20, which accounts for 215,000 individuals, are diagnosed annually, with either type I or type II diabetes. SEARCH for Diabetes in Youth, is a national multi-center study, which was funded and reported by the CDC and National Institutes of Health (NIH)

(2011), attempts to understand more about diabetes among children and young adults in the United States. SEARCH found that each year from 2002 to 2005, over 15,600 individuals younger than 20 years old, were diagnosed with type I diabetes. The most prevalent ethnic group affected in children is the non-Hispanic white group with 24.8 % per 100,000 ("National Diabetes Fact Sheet, 2011," 2011). In 2007, 186,300 school-aged children were diagnosed with diabetes. Diabetes is considered one of the most common diseases for children in this age group (*Overview of Diabetes in Children and Adolescents from the National Diabetes Education Program (NDEP)*, 2011).

Diabetes is also a major financial burden for the United States. The total direct and indirect cost of taking care of people with diabetes is 174 billion dollars. A diabetic can expect medical expenditures to be 2.3 times higher than those without diabetes ("National Diabetes Fact Sheet, 2011," 2011). Diabetes is the leading cause of kidney failure, lower extremity non-traumatic amputations, and new cases of blindness. Diabetes is also a major risk factor for heart disease and stroke ("National Diabetes Fact Sheet, 2011," 2011). Because of these complications it is not surprising that diabetes is the seventh leading cause of death in the United States (CDC, 2011). The Diabetes Control and Complication Trial (DCCT) (1993) from 1982 to 1993 examined individuals with Type I diabetes. Data obtained from the trial showed that improved blood glucose significantly reduces complications caused from poor control. The question that will be explored in this literature review is: Will children, who are less than 18 years of age, who are using CSII, for at least one year, have an improved HbA1c, decreased hypoglycemic episodes, hyperglycemic/diabetic ketoacidosis (DKA) episodes, and improved quality of life (QOL) over those children who use MDI.

In review of the literature, several definitions were used.

Continuous subcutaneous insulin infusion (CSII), delivers insulin through a subcutaneous catheter into the individual via an insulin pump, which is controlled by the individual or care taker. The catheter is changed every two to three days.

Multiple daily injections (MDI) are when the individual gives insulin injections with a subcutaneous needle. Individuals can be classified as mildly, moderately, or severely **hypoglycemic**.

Mild to moderate hypoglycemia is a glucose level less than 70 milligrams per deciliter. The individual is able to recognize the symptoms of hypoglycemia and take the necessary treatment steps (Leiter, Yale, Chiasson, Harris, Kleinstiver, and Sauriol, 2005). **Severe hypoglycemia** is a glucose reading less than 50 milligrams per deciliter and when the individual is unable to treat without the assistance from others. Severe hypoglycemia is associated with seizure and/or loss of consciousness (Weinzimer, 2004).

Diabetic ketoacidosis acidosis (DKA) is caused from hyperglycemia, which leads to acidosis, dehydration, and osmotic diuresis in the individual. If DKA is severe enough the individual will need to be hospitalized for rehydration, intravenous infusion of insulin, and correction of the acid-base imbalance. The range for a fasting blood glucose level is between 110 to 126 milligrams per deciliter (Buttaro et al., 2008).

Hemoglobin A1c (HbA1c) is obtained every three to six months and assists in defining the level of control of diabetes in the individual. In the literature reviews a normal non-diabetic HbA1c is 5.6 % or less. A diabetic has a HbA1c of 6.5 % or higher. Higher HbA1c levels indicate poor control and indicated glucose levels that are above the 126mg/dl ("HbA1c: MedlinePlus Medical Encyclopedia," 2012).

Rapid-acting insulin has an average apparent half-life of 81 minutes and lasts about three to five hours. This insulin is taken five to 10 minutes prior to meals and starts acting in about 15 minutes. **Short-acting insulin** should be given 30 to 60 minutes before a meal and the maximum effect occurs two and half to five hours later. The duration is five to seven hours. **Intermediate-acting insulin** begins to lower glucose levels one to four hours after the injection, and its maximum effect can be seen between four and 14 hours. **Glargine**, also known as Lantus, is a 24 hour basal insulin. This medication is usually given once a day and is used in combination with a short-acting insulin. There are also no peak action times with this medication.

Reduction/improvement of HbA1c means that the HbA1C is a lower number than what it was originally. Significantly lower HbA1c levels indicates improvement in daily glucose levels which correlates with better diabetic control and reduces the risk of complications that diabetes causes ("Patient Education," 2010).

The theoretical framework for this capstone project is the Neuman's System Model. In this model the basic system/structure is not only the child, but the care givers and medical professionals as well. The lines of resistance in the model are to protect the child. The older children can be protected by the care giver and medical professionals. This can be accomplished by providing necessary education and guidance. The younger children are protected by having the care givers and medical professionals assist in administration of insulin, strict glucose control, and meal preparation. Examples of lines of resistance can be education that is provided about CSII in clinical trial from medical professionals, constant contact with children using CSII, and support of the care giver. This enables to child to continue using CSII, but can be flexible based on the needs of the child. The outer two circles of the Neuman's System Model include

the normal line of defense and the flexible line of defense. The flexible lines of defense are able to adjust with the environment. The flexible lines change with the need of the child as in the case of hyperglycemia. Hyperglycemia can be related to poor eating habits. Encouraging proper eating habits can aid in improving hyperglycemia. The stability of the basic structure is dependent on all other factors, whether the factors are internal or external and the ability of the structure to adapt. This is especially true with diabetic children who have a supportive center which possess the ability to give and take. This ultimately improves the child's overall well-being (Alligood, 2010).

Chapter 2: Literature Review

Eligibility. Eligibility for articles included in this literature review consisted of several different criteria. Two main criteria that needed to be present were: the use of CSII in comparison to MDI and had to include children 18 years old or younger as part of the study. Other criteria that needed to be present were reported HbA1c levels with CSII use versus MDI use and hypo-and hyperglycemia episodes with CSII use. Articles that were published before the year 2000, included adults only, or did not examine pertinent data previously mentioned above were excluded. Length of study was not a determining factor whether or not to include the article.

Information Sources. Articles were retrieved from multiple sites. Using the EBSCO research database accessed via Southern Adventist University website, several articles were obtained. Other articles were retrieved from the Diabetes Care and American Academy of Pediatrics on-line archives from previous publications. Ovid Nursing and the National Institute of Health on-line were also used for article reviews.

Search. When searching for articles on-line, the search was limited to articles from 2001 to 2012. Criteria that was used to find articles foremost was CSII in children. Other information used was CSII versus MDI and children, insulin therapy in children, and hypoglycemia in children.

Study Selection. Articles that were included in the review of literature based on either the use of CSII or the comparison of CSII with MDI therapy. Hb1Acs were reported comparing CSII versus MDI use. One article that was included in the review, examined adults and children, but since the article met the other criteria it was included. If articles did not examine the effects of CSII on hypoglycemia, hyperglycemia/DKA and/or QOL, the articles were rejected. Some articles specifically examined the use of CSII in adults. Other articles only reviewed clinical trials using CSII, which were not included.

Chapter 3: Discussion

The articles that were chosen were reviewed and information was gathered to examine the PICOT question. Findings concerning HbA1c, hypoglycemia, hyperglycemia/DKA, and overall effect on the child's QOL were included in this discussion. All of the findings are summarized in Appendix A.

HbA1c findings. Nuboer et al. (2008) examined HbA1c in children, ages four to 16, over a 14 month time frame who used CSII versus MDI therapy. A run-in-phase of three and one-half months was used at the beginning of the study for all participants. This phase consisted of the individual using three short-acting insulin injections before meals and one injection of intermediate-acting insulin at bedtime. After completing the run-in-phase individuals were separated into either into group A using CSII therapy or group B using MDI therapy. Diabetes education, constant glucose monitoring, and nutritional advice were given to individuals

throughout the length of the study. The initial HbA1c for the MDI group was $8.40 \pm 1.06\%$ and at the completion of the study $7.98 \pm 0.57\%$. The CSII group had an initial HbA1c of $8.26 \pm 0.80\%$ and at the completion of the study $7.66 \pm 0.56\%$. Although the results did not have a significant P value, some improvement in lower HbA1c was noted in both groups.

Müller-Godeffroy et al. (2009) studied diabetic children, eight to 16 years of age, from 18 different diabetic treatment centers to compare the effects of switching the participants from MDI therapy, which was not described in the study, to CSII therapy and if any improvement would be noted in the QOL and HbA1c. During the transition from MDI to CSII therapy, the participants were hospitalized from three to seven days for CSII adjustments. The mean HbA1c in the 12-16 age-group at the start of the study was $8.0 \pm 1.56\%$ which was significant with $P < 0.05$ when compared to the mean HbA1c $7.6 \pm 1.33\%$ at the end of the study. The other two age groups four to seven and eight to 11 did show improvements, but the improvements were not significant.

Nabhan et al. (2008) compared glycemic control in toddlers and young children, under the age of five. The participants were initially divided into either the CSII or MDI group. After six months the MDI group was transitioned to CSII therapy. The mean HbA1c was compared when compared to HbA1c at the end of the study and there was significant improvement with HbA1c at the start of the study $8.9 \pm 0.6\%$ versus $8.5 \pm 0.7\%$ at the end of the study, with $P = 0.006$. Nabhan also found that the parents whose children used CSII therapy had significantly lower stress with $P < 0.02$.

Sulmont et al. (2010) found improvement in HbA1c in children less than six years of age over eight years. A cohort design was used to assess whether or not the use of CSII would improve HbA1c and glycemic control long term in children. There were 66 participants, 34 of

which continued on their current MDI therapy and the other 32 participants were started on CSII therapy at the time of diagnosis. During the study, the mean reduction in HbA1c in the CSII group reached statistical significance during year four with $P = 0.015$, year five with $P = 0.010$, and year seven with $P = 0.025$.

Berhe et al. (2006) evaluated the glycemic control, safety and efficacy of continuous subcutaneous insulin infusion with pump therapy in two to seven year olds. The participants were initially on MDI therapy, with at least two injections per day of short-acting insulin and intermediate-acting insulin, for at least one year prior to the study. At the start of the study the participants were transitioned to MDI therapy and continued on the same short-acting insulin. Data was obtained at least one year prior to the study and one year after the study. Berhe found that before the implementation of the CSII therapy, 65 percent of the children had a HbA1c greater than 8.5% and after the study, 76 percent of children's HbA1c was less than 8.5%. Forty percent of the children in this study had a reduction of greater than 0.8% in HbA1c level, which was significant with $P < .001$.

Nelson et al. (2009) examined the HbA1c values during the first 12 months after changing from MDI to CSII therapy in children nine to 18 years of age. The ideal HbA1c of 7.6% was used as a standard when comparing HbA1c. One month prior to initiation of CSII therapy the participants' HbA1c was measured and again at one, four, eight and 12 months. The participants were divided into five groups. Of the 30 participant's ages nine to 18 years old, there were 18 females and 12 males. Group one consisted of five school-age children and three adolescents and achieved the ideal HbA1c within one month of CSII therapy and able to sustain the level over 12 months. Group two achieved the ideal HbA1c at the initiation of CSII, but failed to maintain this at the eight and 12 month HbA1c measurements. Group three was not

able to meet the ideal HbA1c. Group four's HbA1c remained above 8% during the 12 months. The fifth group did not show any constituent trends in either increasing or decreasing HbA1c and all of the HbA1c's obtained were above the ideal HbA1c. Nelson felt that the HbA1c was not achieved by some of the participants because of excessive carbohydrate eating, skipping meals, or stress in the home causing a decrease in parental involvement.

Weintrob et al. (2003) used a randomized open cross over trial with MDI and CSII therapy. Participants, ages eight to 14 years of age, were assigned either to the MDI or CSII group. Participants remained in the groups for three and one-half months and were then transitioned to the opposite therapy. Three months before the study began, participants, along with his or her family, were involved in educational sessions. These sessions included strict glucose monitoring, carbohydrate counting, and insulin adjustments to prevent DKA. The initial HbA1c three months prior to the study was $8.9 \pm 1.0\%$. At the end of the study the mean HbA1c was $8.0 \pm 0.8\%$, which is statistically significant with $P < .001$. However at the end of the study, the CSII HbA1c was $8.0 \pm 0.7\%$ and MDI HbA1c was $8.1 \pm 0.8\%$ with $P = 0.03$. Weintrob stated that the most likely reason for no difference in HbA1c between the two groups was the educational sessions prior to the start of the study.

Edwards et al. (2011) examined the use of CSII to see if this would improve glycemic control in children within one month of the diagnosis of type I diabetes. To be included in this study, participants, ages eight to 18 years of age, had to have a diagnosis of type I diabetes for less than four weeks. The participants either continued using MDI therapy or were started on CSII therapy. HbA1c measurements were taken at the onset of diagnosis, one, three, six, nine, and 12 months. The CSII group showed lower HbA1c values during the first six month interval of the study, but did not maintain this at the 12 month interval.

Doyle et al. (2004) studied whether or not CSII therapy would improve HbA1c in participants, ages eight to 21 years of age, when compared to MDI therapy using short and long-acting insulin, glargine. At the beginning of the study the participants who used MDI therapy was $8.2 \pm 1.1\%$ and the CSII therapy participants HbA1c was $8.1 \pm 1.2\%$. At the end of 16 weeks, those who used CSII therapy had improvement in HbA1c $7.2 \pm 1.0\%$ which was significantly lower compared to the MDI therapy HbA1c $8.1 \pm 1.2\%$. Comparing the mean baseline HbA1c $P < 0.002$ and when the HbA1c was compared between the two groups $P < 0.005$.

Fox et al. (2005) compared an MDI group, using two to three injections per day with rapid-acting and intermediate-acting insulin, with a CSII group for six months. Participants were 12 to 72 months of age. Despite not having significant improvements in HbA1c between the two groups, it is noted that CSII group had slight improvement in the HbA1c with baseline HbA1c of CSII group $7.43 \pm 0.48\%$ and at the end of six months HbA1c $7.24 \pm 0.31\%$ with $P = 0.58$ when compared to the MDI group baseline HbA1c $7.57 \pm 0.27\%$ and at the end of six months $7.46 \pm 0.18\%$ with $P = 0.60$.

Weinzimer et al. (2004) examined the safety of using CSII in young children under the age of seven. All of the participants in this study used CSII therapy. At the end of the study, which was 30 months long, the mean HbA1c for all post-pump visits was $7.1 \pm 0.8\%$. The children older than three years of age seemed to have modest improvement in HbA1c, although not significant when compared to the children younger than three. Weinzimer noted that although there were fewer hypoglycemic episodes and that CSII in young children appears to be safe, the physician's evaluation of the child and caregiver should mandate when CSII therapy is initiated.

McMahon et al. (2004) examined the impact of CSII in children and adolescents, who previously had elevated HbA1c, which was not defined in the study, and recurrent hypoglycemic episodes. HbA1c levels were recorded at the start of CSII therapy and then every three months for a total of 24 months. Prior to initiating pump therapy the HbA1c was $8.3 \pm 0.1\%$ and after initiation of CSII therapy the HbA1c was $7.8 \pm 0.1\%$ with $P < 0.001$.

Wood et al. (2006) examined from 1998 to 2001 why some youth, from the ages of 11 to 17, chose to continue CSII therapy and why others chose MDI therapy. Wood found that the ones who chose MDI over CSII therapy were less adherent to monitoring glucose, eating healthy, and exercising. The youth who continued to use CSII therapy after one year had improvement in the HbA1c. Wood found that individuals, using CSII therapy, who monitored glucose levels frequently had a greater improvement in HbA1c. At the end of the study the HbA1c levels using the CSII therapy was $8.4 \pm 1.2\%$ when compared to those who discontinued CSII therapy and chose to use MDI therapy the HbA1c was $9.4 \pm 2\%$ with $P = 0.01$.

Burdick et al. (2004) examined the effect of CSII on HbA1c, but more specifically those children, less than 18 years of age, who already had CSII, greater than six months, and reasons for less than optimal control. Thirty-five percent of the individuals missed less than one meal bolus per day had a HbA1c of 8% compared to 65 percent of individuals who missed more than one meal bolus per day had a significantly increased HbA1c of 8.8% with $P = 0.0001$. Burdick pointed out that to continue to have optimal control with CSII, the child or adolescent must continue to give meal boluses in the same nature he or she would give an injection of insulin, as in the case of MDI.

Nirmi et al. (2006) examined individuals younger than 40 years of age, who had used MDI therapy for at least one year prior to using CSII therapy. Participants were divided into

three different groups; the pre-pubertal, adolescent, and young adult. HbA1c levels were collected when the individuals were using MDI therapy and during the time the individuals were using CSII therapy. Nimri found that the mean HbA1c levels were lower during the time of CSII therapy than during the MDI therapy with an average reduction of HbA1c by 0.51% with a $P < .001$. The HbA1c during the time of MDI therapy was $8.5 \pm 1.5\%$ and the last HbA1c measurement on CSII therapy was $7.8 \pm 1.3\%$.

Raccach et al. (2009) examined the use of a continuous glucose sensor in diabetic patients with a HbA1c greater than 8% at the start of the study to see if there was any improvement in using CSII therapy with the sensor compared to CSII without using the sensor. The study included adults and children with 51 of the 132 participants being children. Those in the CSII sensor group had significantly lower HbA1c levels than the CSII non-sensor group with HbA1c levels.

Plotnick et al. (2003) examined children and adolescents, ages four to 18 years of age, in a trial for 28 months with CSII and MDI therapy. HbA1c levels were collected for six to 12 months prior to the study and every three months after the study began. During the three to six months the children and adolescents with CSII therapy had HbA1c levels that were significantly improved when compared to the start of CSII. When reviewing the HbA1c at the six month mark there was a notable trend of increasing HbA1c. This rise in HbA1c was thought to be related to either age or the length of time that the child or adolescent had type I diabetes.

Hypoglycemia. Nuboer et al. (2008) also found a decrease in severe hypoglycemic events (average of 0.29 episodes), which indicates a threefold reduction of severe hypoglycemic events that occurred in the CSII group. Sulmont et al. (2010), when comparing CSII to MDI groups, noted fewer episode of hypoglycemia with $P = .016$. In the Weinzimer et al. (2008)

study the rates of hypoglycemic episodes were similar between the two groups. However, it was noted more hypoglycemic episodes occurred during the day rather than at night which is consistent with more activity. The risk of hypoglycemia at night related to CSII use continues to be a concern for many physicians and practitioners, but this study found that hypoglycemia was more common during the day. Wilson et al. (2005) noted that one CSII participant and one MDI participant suffered severe hypoglycemic episode, but the CSII participant also had similar episodes while using MDI prior to the study.

The non-randomized trial by Weinzimer et al. (2004) found significant improvement in hypoglycemia. In the study, severe hypoglycemia rates decreased as a whole by 53%, from 78 events per 100 patient-years to 37% per 100 patient-years with $P = .02$. The greatest improvement noted was in the severe hypoglycemia events occurring in children three to five years of age, whose rates decreased by 79%, from 141 to 29 events per 100 patient-years $P < .001$. Weinzimer pointed out that using CSII in younger children is safe and effective and should be considered as a treatment plan.

The retrospective study by Nimri et al. (2006) also showed improvement in hypoglycemia. There were no episodes of severe hypoglycemia in the pre-pubertal group, but in the adolescent and young adult groups, the number of severe hypoglycemic episodes per 100 patient-years decreased significantly from baseline to one year after initiation of CSII therapy with $P < .01$ and $P < .05$, respectively. Berhe et al. (2006) also noted significant decrease in hypoglycemia for children who used CSII with a $P < .001$. Plotnick et al. (2003) examined the events of hypoglycemia prior to CSII therapy and with CSII therapy. Plotnick found there were 14.3 events per 1,000 patients versus 6.6 per 1,000 patients.

Hyperglycemia/DKA. Nuboer et al. (2008) also found that with CSII therapy there were only two episodes of DKA when compared to the MDI group of four episodes. Edwards et al. (2011) found that amount of time spent in hyperglycemia was decreased 21% in the CSII group compared to 36% in the MDI group with a $P=0.04$. When Weinzimer et al. (2007) compared aspart insulin versus lispro insulin it was noted that the rate of hyperglycemia was decreased by 11% in the aspart group and 17 % in the lispro group. Even though CSII was not compared to MDI, the results still indicate a decrease in hyperglycemia episodes. In 2006 Nimri divided children and adolescents into groups by age and found the DKA of the pre-pubertal age group with a $P = .057$ was related to pump technicality. The other two age groups, however, did not have any DKA episodes. Wilson et al. (2005) found when comparing the hyperglycemia rates between CSII and MDI therapy, there was no difference noted between the two groups.

Quality of Life. Hilliard et al. (2009) found that youth had more issues with anxiety and depression prior to starting CSII therapy. At the end of the study the youth had more improved QOL, improvement in depression and anxiety compared to the youth who used MDI therapy. It was also found that children, with two or more adults in the home, had a more improved QOL than children with only one parent which was obtained from the Parent Report Questionnaire.

Müller-Godeffroy et al. (2009) examined if CSII would provide flexibility in lifestyle and affected family burden. The Overall Diabetes Burden for parents with younger children reported less of a burden for themselves when the child used CSII. Parents of school-aged children and adolescents also reported less stress for themselves. Weintrob et al. (2003) found that participants of the study were more satisfied with CSII therapy rather than MDI therapy. Wilson et al. (2005) found improvement in the QOL prior to CSII therapy and after completion of the

study for those participants in the CSII group, but when compared to the MDI group there was no significant difference.

Fox et al. (2005) examined the burden of disease between the mothers of the CSII and MDI group. Fox found that the mothers of the MDI group felt more of an impact on life from the diabetes. Fathers were also examined and it was found that those fathers of the MDI group felt more psychological distress than those fathers who children used CSII. However, McMahon et al. (2004) did not see any improvement in the QOL of either the participant or the care giver. However, participants did report increased self-efficacy scores with CSII therapy.

Limitations. There were several limitations noted throughout this literature review. The most notable limitation is the small sample sizes that were studied. Partly, this is related to the fact the studies involved children. Other limitations noted in some of the studies was the length of time - one study was only 16 weeks long. Not all of the studies examined the same parameters as described in the PICOT question. There were also fewer articles dealing with CSII therapy including children over the last two to three years, therefore a majority of the data is included from 2002 till present. Very few magazines are targeted towards CSII therapy and therefore many articles came from Diabetes Care. Insurance companies can also be a limitation in this study because of the cost of CSII therapy, which is very expensive, versus what the insurance company will pay and provide for the patient. Also, retrieving some articles from on-line sources required payment for articles being used and because of this, it excluded some articles from being used.

Chapter 4: Conclusions

By examining all of the articles, specifically targeting Hb1c levels, hypoglycemia, hyperglycemia/DKA, and QOL certain conclusions can be made. HbA1c, according to the

majority of the literature reviewed, improves with CSII therapy when compared to MDI therapy. Yet, it was noted that the CSII therapy improved significantly when the child and/or caregiver was educated and contacted by medical professionals often. This supports the theory by Neumann that the system shifts with the environment, but with strengthening of the lines of defense the core becomes stronger. No specific age group improved more with CSII therapy with regard to HbA1c than another group. Each study had different age groups that did better than the other, but at this time it cannot be predicted that the age of the child or adolescent guarantees better glycemic control over other ages.

When evaluating hypoglycemia and hyperglycemia/DKA, the episodes and the percentages of these events are decreased with CSII therapy. Only a small percent of the studies showed no difference between the two groups. This also could be linked with the fact that education was received about nutrition and checking glucose levels often throughout the day and night hours. It was noted by several articles that increased amounts of glucose checks decreased the risk of these events. Some of the studies did show some improvements in the QOL of either the child or the caregiver. Although several studies commented that a majority of the participants wanted to continue on CSII therapy after the study was completed rather than MDI therapy.

It was noted in several of the studies that children and adolescents required less insulin with CSII therapy when compared to MDI therapy. Also, the BMI decreased with the use of CSII, which has been postulated by many to actually increase with CSII use. The ultimate goal of CSII therapy is to provide strict glycemic control while providing flexibility and normalcy to the child and adolescent. The PICOT question that was asked at the beginning of this literature review can be supported by the evidence provided in the articles presented. One main

requirement to be able to meet this improved glycemic control is constant support and education.

Without control, improved glycemic control cannot be achieved.

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Appendix A

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| Nuboer et al., 2008 | Examining the changes in the QOL and the impact of the disease in CSII vs. MDI use in children | N = 38 Group A = 19 Group B = 19 | Randomized, prospective parallel design. | HbA1c with MDI use at start and end of study: 8.40 ± 1.06 compared to 7.98 ± 0.57 . |
| | | | | HbA1c with CSII use at start and end of study: 8.26 ± 0.80 compared to 7.66 ± 0.56 |
| | | | | No significant improvement in Pediatric Quality of Life ($p < 0.05$). In CSII group, severe hypoglycemic episodes decreased an average of 0.29 percent indicating a threefold reduction. MDII = 4 episodes of DKA compared with CSII with only two episodes. |
| Nabhan et al., 2008 | Compare diabetes control, neurocognitive functioning, and behavioral/family functioning in toddlers and young children treated with CSII therapy versus intensive insulin injection therapy (IIT). | N = 35 Age = 3.7 ± 0.7 Males = 17 Females = 18 Duration of diabetes = 1.6 ± 0.6 Hemoglobin A1c (HbA1c) = 8.8 ± 0.6 Body mass index (BMI) = 79.4 ± 17 | Randomized Prospective Study with mixed method design | Mean HbA1c = $8.9 \pm 0.06\%$. ANOVA showed significant changes in HbA1c over time ($p = 0.007$). |
| | | | | No difference between CSII and IIT ($p = 0.518$) or interaction between time and group ($p = 0.454$). HbA1c compared with the baseline mean decreased significantly over the yearlong study in both groups (8.9 ± 0.6 versus $8.5 \pm 0.7\%$, $p = 0.006$). |
| Sulmont et al., 2010 | Assess the long-term metabolic outcomes in children who were diagnosed with diabetes less than six years of age. | N = 66 children Group A (MDI therapy) = 34 Group B (CSII therapy) = 16 | Cohort study | HbA1c levels in group B (CSII) were lower than Group A (MDI) during the eight year follow up. During year 1 HbA1c in group B $< 6.5\%$, $P = .046$. The HbA1c compared between the two groups was statically significant at 4 years with $P = .015$. |
| | | | | Group B had fewer hypoglycemic episodes than Group A ($P = .016$). |
| | | | | No difference in DKA between the two groups. |

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| Berhe et al., 2006 | Evaluate the glycemic control, safety, and efficacy in CSII in children 2-7 years old | N= 33 | Retrospective Study | HbA1c before (65% of the children was >8.5%) and after (76% of children was <8.5%). 40% of the children had a reduction of >0.8% in HbA1c level. P<.001. |
| | | | | Hypoglycemia significantly reduced with a P < .001. Also no reported seizures with CSII. |
| Nelson et al., 2009 | Examine the HbA1c values during the first 12 months of CSII in children 9-18 years of age. | N= 30 Males= 12 Females=18 | A repeated measures design guided study. | Group 1 : 5 school-aged children and 3 adolescents achieved HbA1c of 7.6% within 1 month of CSII therapy and sustained the level over 12 months. Prior to the study 4 of the 8 had a HbA1c of 7.6% or less. |
| | | | | Group 2: 5 school-aged children and 4 adolescents. Three of the individuals already had HbA1c less than the target goal. The other 6 individuals actually had a HbA1c above the target goal. |
| | | | | Group 3: 1 school-aged female and 1 adolescent female. The school-aged met the HbA1c requirement, but the adolescent did not. |
| | | | | Group 4: Showed minimal change in HbA1c but was 8%. |
| Weinzimer et al., 2007 | Examine whether it is safe to use lispro or aspart insulin in CSII in children and adolescents. | N=298 children and adolescents Aspart N= 198 Lispro N= 100 | 16 week, open label, multicenter parallel-group. | The rates of hypoglycemic episodes were similar between the two groups. More hypoglycemic episodes occurred during the day rather than at night which is consistent with more activity. |
| | | | | In both groups the incidence of hyperglycemia was lower (aspart 11% and lispro 17%). |

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| Weintrob et al., 2003 | Compare the efficacy and feasibility of CSII with MDI in children with type 1 diabetes. | N= 23 children (10 males) Ages 9.4 to 13.9 years with type 1 diabetes. | A randomized crossover design | HbA1c was significantly lower from the start of the study to the first 3 month interval with HbA1c $8.9 \pm 1.0\%$ vs. $8.0 \pm 0.8\%$. This change is thought to be related to increased glucose monitoring and education session prior to the study. |
| | | | | QOL: The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Diabetes Quality of Life Questionnaire for Youth (DQOLY) were used at the beginning and at the end of each treatment arm of the study. DTSQ satisfaction scale at beginning of study was 71.9 ± 14.5 and was 74.8 ± 13.5 at the end of the study. Overall scores of DTSQ at beginning of MDI arm, 21.9 ± 3.8 and at the end of the CSII arm 30.6 ± 3.7 , ($P < .001$). No difference noted in the DQOLY with satisfaction scale 71.9 ± 14.5 at beginning of study and 73.5 ± 14.0 at the end of the study. |
| Edwards et al., 2011 | Examine if starting CSII at the time of onset of diabetes preserved C-peptide secretion and had an improvement in glycemic control. | N=24 | Prospective randomized pilot trial | HbA1c in the CSII group were lower are 6 months, but did not maintain this at the 12 month interval. |
| | | | | Hyperglycemia episodes were decreased in the CSII group (21% vs. 36%) $P = 0.04$ |
| Fox et al., 2005 | Assess the effects of insulin pump therapy on diabetes control and family life in children 1–6 years old with type 1 diabetes. | N = 23 Males = 13 Females = 10 | Randomized control trial. | HbA1c values were similar between CSII and current therapy groups at baseline (7.43 ± 0.48 vs. 7.57 ± 0.27 , CSII vs. current therapy, at 3 months (7.20 ± 0.29 vs. 7.46 ± 0.22), and at 6 months (7.24 ± 0.31 vs. 7.46 ± 0.18). |
| | | | | QOL: The pediatric Diabetes Quality of Life Scale, which was designed for this study was used examine how the child's diabetes effected the parent(s) interaction with the child or the child's behavior. QOL was examined prior to the study and again at 6 months. |

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| McMahon et al., 2004 | Determine the impact of insulin pump therapy on key parameters of diabetes management including quality of life in children and adolescents with Type 1 diabetes mellitus (T1DM). | <p>N= 100 M = 41 F = 59 Age < 12 = 40 Age > 12 = 60</p> | Design of study not mentioned. | <p>Post pump HbA1c: 7.8 (\pm 0.1)%. (Range 6.1–10.4%) ($P < 0.0001$) Ages < 12 HbA1c pre-pump vs. post pump: 8.3 \pm 0.2% vs. 7.5 \pm 0.1% ($P < 0.001$). Ages < 12 HbA1c pre-pump vs. post pump: 8.4 \pm 0.1% vs. 7.9 \pm 0.1%.</p> <p>Pre pump severe hypoglycemia (events/100 patient years): for < 12 years = 25.9 and > 12 years = 37.5. Post pump severe hypoglycemia for (events/100 patient years): < 12 years = 8.3 and > 12 years = 13.5.</p> <p>Modified version of the Diabetes Quality of Life Instrument (DQOL) was used (not defined in the study). 43 questionnaires were gathered. It was found the QOL prior to insulin pump therapy was 63.5 \pm 2.1 and after the study was 68.6 \pm 2.1.</p> |
| Nimri et al., 2006 | Compare by age and glycemic control continuous subcutaneous insulin infusion with multiple daily injections in youth with type 1 diabetes. | <p>N= 279 Prepubertal= 23 with age range 1.6–8.6 years. Adolescents= 127 with age ranges 9-17 years. Young adult = 129 with ages ranges 17-40 years.</p> | Retrospective paired study longitudinal analysis. | <p>Mean HbA1c: Significantly lower during CSII therapy than during MDI therapy (-0.51%; $P < .001$) for the entire cohort. Prepubertal (-0.48%; $P < .05$); Adolescent (-0.26%; $P < .05$); Young Adult (-0.76%; $P < .001$) groups</p> <p>No episodes of severe hypoglycemia in the prepubertal group. Adolescent and young adult groups, the number of severe hypoglycemic episodes (per 100 patient-years) decreased significantly from baseline to 1 year after initiation of CSII therapy ($P < .01$ and $P < .05$, respectively).</p> |
| Raccach et al., 2009 | Whether CSII will show improved metabolic control and evaluate change in glycemic variability. | <p>N = 132 Children = 51 Adults = 81</p> | Not described | <p>HbA1c were significantly lower during CSII therapy than during MDI therapy (-0.51%; $P < .001$) for the entire cohort. Pre-pubertal (-0.48%; $P < .05$) Adolescent (-0.26%; $P < .05$) Young Adult (-0.76%; $P < .001$) groups</p> |

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| Plotnick et al., 2003 | Evaluate safety and effectiveness of CSII therapy in children and adolescents with type I diabetes. | N = 95 F = 52 M = 43 | Not described | HbA1c was significantly improved after CSII therapy was started ($P = 0.03$). At 6 months trend noted in HbA1c to be increasing with ($P < 0.001$). |
| | | | | Hypoglycemic events decreased after CSII therapy started. 14.3 per 1,000 patient months prior to CSII and 6.6 per 1,000 patient months after CSII. |
| | | | | One episode of DKA prior to CSII and one episode during CSII. |
| Burdick et al., 2004 | Identify causes of poor glycemic control in youths who use CSII therapy | N = 48 F = 23 M = 25 | Not described | HbA1c in the 13 to 15 year old age group had highest HbA1c of 8.8 % and highest number of missed meal boluses. Children < 13 had best HbA1c of 8.4%. |
| Wood et al., 2006 | Examine reasons for CSII discontinuation and predictors of insulin pump success. | N = 161 | Not described | HbA1c baseline prior to CSII therapy was 8.4 ± 1.4 and after 1 year of CSII therapy was 8.0 ± 1.3 . Those who discontinued CSII therapy had HbA1c at baseline prior to trying CSII was 8.5 ± 1.4 and after discontinuation 8.6 ± 1.3 . |

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| Müller-Godeffroy et al., 2009 | Investigate different psychosocial features which might be relevant for patients and parents using CSII therapy | <p>N = 117 Males - 64 Females - 53 Child age 10.5 ± 3.7 years 8-11 years-25 12-16 years- 63 Parents of 4-7 year olds- 29 See table 1 pg. 495</p> | Pilot Study | <p>HbA1c range in 4-7 age-groups prior to study and after: 3.7 to 10.1 compared to 4.7-9.4.</p> <p>HbA1c range in 8-11 age-groups prior to study and after: 7.6 ± 0.78% compared to 7.4 ± 0.85%.</p> <p>HbA1c range in 12-16 age-groups prior to study and after: 8.0 ± 1.56% compared to 7.6 ± 1.33%. Significant with P < 0.05.</p> <p>No significant decrease in severe hypoglycemia.</p> <p>KINDL_DM: Scores increased significantly in medium effect size adolescents and large effect size in school-ages children and younger children. PIP: Decrease in some of the subscales, but did not meet previously defined significance level of P < 0.005.</p> <p>HFS-P Worry scale: Significant decrease in hypoglycemia –related worries. Effect size moderate to large.</p> <p>HFS-P Behavior Scale: No decrease in this scale and less frequency of feeding behavior problems. Effect size moderate to large.</p> <p>Overall Diabetes Burden: Parents of younger children reported significantly less burden for themselves.</p> <p>Mean t0=3.62 ± 1.06, mean t1 = 3.12 ± 1.1) and to the child with diabetes (mean t0 = 3.00 ± 1.12, man t1 = 2.36 ± 0.76.</p> <p>Difference statistically significant with (Z = -3.23, -4.15, P< 0.01, Wilcoxon test, two-tailed testing), with moderate to large effect size (d= 0.5 – 0.8).</p> <p>Parents of school-age children and adolescents reported significant less Overall Diabetes Burden in regard to themselves (8-11 years: mean t0 3.54 ± 0.92, mean t1= 2.64 ± 0.87, Z= -3.57, P < 0.001; 12-16 years: mean t0 = 2.70 ± 1.01, mean t1 = 2.40 ± 0.82, Z= -2.36, P < 0.05)</p> <p>Child with diabetes 8-11 years mean t0= 3.50 ± 0.95, mean t1 = 2.54 ± 1.03, Z= -3.24, P< 0.01 12-16 years: mean t0= 3.07 ± 1.02, mean t1 = 2.64 ± 1.01, Z= -3.05, P < 0.01).</p> <p>Effect size large in school-aged children and moderate in adolescents.</p> |
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| Hilliard et al., 2009 | Investigate the changes in quality of life and of impact of disease by either CSII or MDII | <p>N=77</p> <p>4-7 years old: 9</p> <p>8-12 years old: 7</p> <p>13-16 years old: 7</p> <p>Males: 17</p> <p>Females: 21</p> | Open parallel, randomized controlled perspective comparative study | <p>Significantly decreased HbA1c from 8.34 to 7.82 (-0.52%, p= 0.001).</p> <p>Within-patient analysis showed a decreased HbA1c at the end of the 7-10.5 month CSII period by 0.22% (p=0.02) while using an average of 0.27U/kg/d less insulin, p< 0.001.</p> <p>Children with HbA1c levels >8% at the start of CSII (means 9.1 ± 1.0) showed a decrease in HbA1c to a mean of 8.56 ± 1.0 after 7 -10.5 months of CSII 9 p=0.001).</p> <p>QOL:</p> <p>The Diabetes Quality of Life for Youth Scale (DQOL-Y) is a 53 -item questionnaire that was used to examine how diabetes impacted the individuals life, concern about having diabetes, and satisfaction with life. The QOL improved most in children, who had more anxiety, depression, longer illness duration, and had at least two adult caregivers in the home.</p> |
| Wilson et al., 2005 | Prospectively conduct a 1-year, randomized, controlled, open-label feasibility trial comparing CSII with MDI in young children with diabetes. | <p>N= 19 subjects</p> <p>CSII group = 9</p> <p>MDI group = 10</p> | Randomized 1-year feasibility trial | <p>Baseline HbA1c: Mean HbA1c was 8.0% ± 0.8.</p> <p>HbA1c post study: There was no significant difference (P = 0.44, Student's t test) in the change in HbA1c between the two groups (-0.21 ± 0.67%, CSII; 0.04 ± 0.71%, MDI).</p> <p>None of the participants developed DKA</p> <p>One CSII and one MDI participants suffered severe hypoglycemic episode, but the CSII participant also had similar episodes while using MDI prior to study.</p> |
| Doyle et al., 2004 | Compare the efficacy of CSII to MDI with glargine in lowering HbA1c levels in children and adolescents with type 1 diabetes. | N=32 | Randomized, prospective trial | <p>HbA1c levels at baseline:</p> <p>Similar in the glargine and CSII groups (8.2 ± 1.1 vs. 8.1 ± 1.2%, respectively, P = 0.89). After 16 weeks of glargine treatment, HbA1c levels (8.1 ± 1.2%) were not significantly different from baseline.</p> <p>HbA1c levels fell sharply in the CSII group to 7.2 ± 1.0 at 16 weeks (P < 0.02 vs. baseline and P < 0.05 vs. glargine group).</p> |

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| Weinzimer 2004 | Analyze the CSII efficacy and safety data in very young children with type 1 diabetes from our Diabetes Clinic database. | <p>N= 65 Gender, F/M= 38/37 < 3 years= 11 3-< 5 years = 26 5-< 7 years = 28</p> | Non-randomized uncontrolled design. | <p>QOL: The pediatric Diabetes Quality of Life Scale, which was designed for this study was used examine how the child's diabetes effected the parent(s) interaction with the child or the child's behavior. QOL was examined prior to the study and again at 6 months.</p> <p>Mean HbA1c fell from $7.4 \pm 1.0\%$ in the year before pump initiation to $7.0 \pm 0.9\%$ at 12 months after pump initiation ($P < .001$).</p> <p>Glycemic control improved during the follow up period; mean HbA1c of $6.8 \pm 0.6\%$ at 3 years of follow-up ($P = .003$ from prepump values) and $6.5 \pm 0.9\%$ in the 6 children who amassed 4 years of follow-up. The mean HbA1c for all postpump visits was $7.1 \pm 0.8\%$, and the mean for each subject's most recent visit at the time of data closeout (at a mean duration of follow-up of 30 months) was $7.0 \pm 0.9\%$ ($P < .02$ from prepump values).</p> <p>HbA1c levels were most notable in children < 3 years old, who had a prepump value of $7.9 \pm 1.1\%$ to a mean postpump value of $6.9 \pm 0.9\%$ ($P = .01$). "Older" children experienced a more modest improvement, from $7.4 \pm 0.9\%$ to $7.2 \pm 0.6\%$ in the 3 to <5 years group, and from 7.2 ± 0.9 to $7.1 \pm 0.9\%$ in the 5 to < 7 years group, neither of which reached statistical significance.</p> <p>SH (severe hypoglycemia) rates decreased in the group as a whole by 53%, from 78 events per 100 patient-years to 37 per 100 patient-years ($P = .02$). The greatest improvement in SH occurred in the children 3 to < 5 years of age, whose rates decreased by 79%, from 141 to 29 events per 100 patient-years ($P < .001$).</p> <p>DKA: postpump period was 4 episodes per 100 patient-years.</p> |
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